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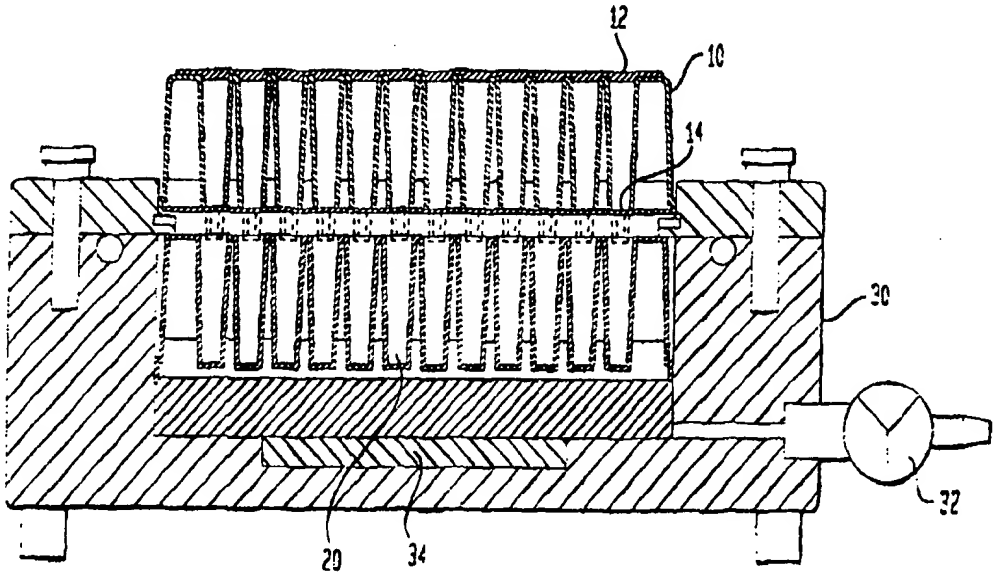

(57) Abstract

The device of the present invention is comprised of a multi-well filter bottom plate (10) with a selectively permeable barrier (14) comprised of a porous substrate having an oleophobic chemical surface. The filter plate (10) is used to contain multiple simultaneous chemical reactions. The selectively permeable barrier (14) holds the reaction mixtures in the wells until such time that it is desirable to remove some or all of the well contents. The selectively permeable barrier (14) is designed or selected to have a lower effective critical surface energy than the surface energy of the reaction mixture. The reaction wells can be drained by lowering the effective surface tension of the reaction mixture; this can be accomplished by altering the surface tension of the reaction mixture with the addition of a surface tension lowering composition. Alternatively, the reaction wells can be drained by the application of a pressure differential across the selectively permeable barrier, or by the application of centrifugal force.

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Title: **DEVICE AND METHOD FOR SIMULTANEOUS MULTIPLE CHEMICAL SYNTHESES**

Background of the Invention

Current practice involves the use of multi-well devices with a non-porous base which are not permeable nor can they be easily made permeable. The use of multi-well devices without a porous substrate results in cumbersome and time consuming manipulations (either in a manual mode or an automated mode) since the operator (or instrument) often needs to transfer the contents of the wells (i.e. the reaction medium) to another device (e.g. filtration device) for further processing upon completion of the desired chemical reaction(s). This is particularly inefficient and cumbersome for the formation of desired reaction product(s) which involve multiple or single chemical steps with associated isolation and purification processes as well as syntheses which entail the use of small or minute quantities of reactants and solvents.

Devices with 8 and 96-wells made from porous PTFE (polytetrafluoroethylene) as well as single-well glass devices containing porous PTFE frits or porous glass frits have also been used. Such porous materials have an unfavorable critical surface energy for many of the solvents and reaction conditions typically desirable in chemical syntheses and so do not retain these solutions.

Other devices use a limiting number of multiple, glass cylindrical reaction vessels with a porous-glass base. Such apparati are not readily amenable to large-scale automation

and are incompatible with much of the instrumentation, equipment, and technology currently adopted and in use by the pharmaceutical and biotech industries.

The use of devices and systems which employ electromechanical valves in order to "hold-up" solvent mixtures until reaction has taken place has also been disclosed. Such devices are expensive and cumbersome and require considerable care, particularly cleaning if they are to be reused.

Summary of the Invention

The present invention allows for an efficient, versatile, and tailored approach for conducting, simultaneously or otherwise, any number of chemical reactions involving single-step or multi-step syntheses and associated processes by use of a single device. Controlling the retention of the reaction mixture by tailoring the energetic interplay among the critical surface energy of a porous substrate(γ_c), the surface tension of the reaction medium(γ_{mix}), and a deliberate change in the surface tension of the reaction medium(γ_{app}) allows for the completion of desirable chemical reactions and further processing of such chemical reactions (such as product(s) isolation and purification processes) in an efficient manner suitable for cycling in multistep syntheses by use of a single device.

A reaction-well device and method for simultaneously conducting multiple chemical reactions in series or in-parallel, or a combination of parallel and serial manipulations, is described. The chemical reactions can be of synthetic origin or biochemical origin or a combination of synthetic and biochemical transformations. The volume of the unit well(s) in the reaction-well device can vary from less than microliter(μL) to more than liter(L) volumes and each well can be of the same or differing volumes depending upon the quantity of the reactants used or the quantity of product(s) desired. The nature of the chemical reactions

carried out in the device can be of a homogeneous phase, e.g. a single solution or liquid phase, or a heterogeneous phase, e.g. a liquid phase and a solid phase, a liquid phase and a gas phase, two or more immiscible liquid phases, or any combination of solid, liquid and gas phases. The chemical reaction conditions employable with the multi-well device will depend upon the materials of construction of the device as well as the reaction conditions necessary for obtaining the desired product(s) and include but are not limited to: elevated, ambient and low temperatures and pressures; acidic, basic and neutral aqueous and organic solvents; inert and reactive gases.

A novel feature of the device and methodology of the present invention is a selectively permeable barrier encapsulated within the reaction-well device. This acts essentially as a molecular flow control switch. Permeability through the barrier can be selected for or designed through the interplay of energetics between the critical surface energy of a porous substrate(γ_c), the surface tension of the reaction medium(γ_{mix}), and a deliberate change in the surface tension of the reaction medium(γ_{app})such that the difference in γ_{app} and γ_c provides for or inhibits spontaneous flow of the reaction medium through the permeable barrier. This selectively permeable barrier "holds-up" or retains the reaction mixture in the wells of the multi-well device until such time that it is desirable to remove some or all of its components through the selective barrier. Removal of the reaction medium or components from the reaction medium is accomplished by manipulation of the effective difference between γ_{app} and γ_c or by the application of a pressure differential across the barrier. Methods of manipulating the effective difference in γ_{app} and γ_c include changing reaction medium or reaction conditions.

The present invention allows for a greater number of simultaneous chemical syntheses to be operating at any one time depending upon the array of wells in the multi-well reaction-

well device, as well as operating under a wide range of chemical reaction conditions, using many of the organic solvents typically used in traditional synthetic chemistry without the need of additional filtration and isolation devices and associated processes. Furthermore, the present invention may include a means for selectively retaining desirable reaction product(s), i.e. a mechanism for further processing of chemical reactions for targeted product(s) isolation and purification. Such a means includes, but is not limited to, the use of additional solid media which selects for the targeted product(s) for isolation and further purification. The present approach also allows for the "modular" combination of one or more filter plates (for chemical reaction(s), product isolation(s) and purification) for further versatility and efficiency as well as for automation.

The present device and methodology are readily amenable to automation by design or by utilizing commercially available instrumentation, equipment, and technology currently adopted by the chemical, pharmaceutical and biotech industries and related industries.

The device described in the present invention is disposable, if desirable, or reusable with minimal maintenance and care.

Industrial Applications

The present invention has applications in the areas of combinatorial chemistry, peptide and nucleotide library formation, and phage display libraries. Additionally, the present invention has applications in diagnostic or biological assays in order to identify, for qualitative or quantitative purposes, specific predetermined compounds, target molecules, and microbes (viral, bacterial and the like).

The present invention is amenable to automation either by design or by using existing instrumentation and equipment such as that commonly used in the chemical, pharmaceutical, biotech, and related industries.

These and other features of the invention may be more fully understood by reference to the following drawings.

Brief Description of the Drawings

Figure 1 is a sectional-side view of a 96-well device, i.e. a 12 x 8 array of reaction cells, used in the present invention.

Description of the Invention

During the course of this description like numbers will be used to identify like elements accordingly to the different figures that illustrate the invention.

As illustrated in figure 1, the device of the present invention includes: (1) A filter plate **10** with one or more reaction wells and a filter plate cover **12**. The plate cover may have associated with it a mechanism and means for attachment (integral or separate to the plate cover) of the cover to the filter plate for operation of the device under a variety of reaction conditions such as elevated or lowered temperatures and pressures. The plate cover may have associated with it a mechanism and means of attachment of a gas manifold (integral or separate to the plate cover) for reactions operating under a variety of atmospheres (inert or reactive) such as argon and nitrogen. In another embodiment, the plate cover may have attached to it (integral or separate to the cover) solid-phase synthetic supports (of a similar or differing array to that of the filter plate) that protrude into the volume of the wells of the filter plate for chemical reaction under a variety of reaction conditions. (2) A

collection plate **20** with one or more wells, preferably corresponding in number to the number of wells on the filter plate. (3) A manifold **30** to house the filter **10** and collection **20** plates as well as to provide a means of introducing a vacuum or gas (e.g. 3-way valve **32**). The manifold may also have a heat source **34** for operation at elevated temperatures and/or a heat sink 34 for operation at lower temperatures. Associated with the manifold may be clamps and seals for attachment of the filter plate (and cover) and collection plate for operation of the device under a variety of reaction conditions such as elevated and lower temperatures and pressures as well as a means and mechanism for agitation of the chemical reaction(s) and for device automation. In another preferred embodiment, the present invention contains a heater jacket around the reaction filter bottom plate as well as a plate seal block which is attached to the bottom of the manifold so that the whole system can be placed on a table top shaker instead of being placed into an oven or incubator. Materials for construction of the multi-well device will depend upon the reactants used and the conditions necessary for the formation of desired product(s) and include but are not limited to: polymeric materials (synthetic or natural), metals, ceramics, and glasses or any combination thereof.

The reaction-well filter plate **10** contains at its base a porous material or substrate **14** having an oleophobic (or low energy) chemical surface. The porous substrate itself may be a filter or membrane of synthetic or natural origin, for example, glass fiber filters GF/x where x= A, B, C, D, and F (designating different porosities); polypropylene; nylon; PTFE, PVDF,; and cellulose. The oleophobic chemical surface is inherent in or applied to the porous substrate and is designed or selected to have lower surface energy(γ_c) than the reaction medium(γ_{mix}) which it will come in contact with under the reaction conditions leading to the desired product(s). This low energy or oleophobic surface repels many of the more commonly used solvents in synthetic chemistry, i.e. it inhibits spontaneous solvent flow or

seepage through the porous substrate. As such, the oleophobic chemical surface confers selective permeability to the porous substrate. The oleophobic surface of the porous substrate "holds-up" solvents or other solutions in the multi-well device until it is intentionally desirable to remove some or all of the contents of the multi-well device through the porous substrate.

The critical surface energy of the porous material(γ_c) is an empirical parameter characteristic, in part, of the porous substrate. It depends on such factors as the surface energy of the materials of construction of the porous substrate, the nature and degree of the substrate porosity, the morphology of the porous substrate, the nature and volume(V) of liquid intended for the porous substrate to hold up as well as the temperature(T) and duration(t) of liquid exposure. Typically, the temperature and duration of liquid exposure to the porous substrate can be selected to be typical conditions characteristic of many chemical reactions or characteristic of the reaction condition(s) of interest. The critical surface energy of the porous substrate can be readily determined by exposing the substrate to some fixed volume of liquid(s) or mixture of liquids of known or determined surface tension. Such liquids could include miscible mixtures of one or more alcohols and water of known or determined surface tension as well as homologous series of hydrocarbons (e.g. pentane, hexane, heptane, octane, etc.) or fluorocarbons, or the like with known or determined surface tension. For example the critical surface tension of a porous substrate that allows flow through or seepage of 5 mL(V) of n-pentane (surface tension at 20 °C = 16.0 dynes/cm) and n-hexane (surface tension at 20 °C =18.4 dynes/cm) over a period of 4 hours (t = 4 hrs.) at 20 °C (T = 20 °C) but, holds-up or provides a barrier towards n-heptane (surface tension at 20 °C = 20.1 dynes/cm) and n-octane (surface tension at 20 °C = 21.6 dynes/cm) under identical conditions would be: $18.4 \leq \gamma_c \leq 20.1$ (in dynes/cm at T = 20 °C, V = 5 mL and t = 4 hrs.)

Depending upon the surface tension of the reaction medium associated with the chemical reaction of interest, γ_c may be selected for or designed by the methods described previously.

Many porous materials of synthetic or natural origin have characteristic γ_c's of sufficiently low energy relative to the surface tension of the reaction medium (γ_{mix}) characteristic of many but not all of the desirable chemical reactions such that it is unnecessary to confer additional oleophobicity to the porous material. Providing that γ_{mix} is determined or known then those substrates with appropriate γ_c (e.g. porous PTFE) can be selected for and incorporated into devices of the present invention. Such selected porous substrates, with appropriate γ_c 's, repel or inhibit flow of the reaction medium through the porous substrate. Removal of all or part of the contents of the multi-well device through the porous substrate may be accomplished by the application of a pressure differential across the porous substrate or by lowering the surface tension of the reaction medium as described above.

Many porous substrates (synthetic or natural) have characteristically unfavorable γ_c's such that the difference in energies between γ_{mix} and γ_c provides for spontaneous flow or seepage of the reaction medium through the porous substrate. Favorable energetics and a desirable interaction so that the reaction medium does not flow or seep through the porous substrate can be accomplished by, for example: (1) lowering the effective γ_c of the porous substrate by conversion to an oleophobic or low energy surface or coating the surface of the porous substrate with one or more oleophobic compositions. (2) Increasing the surface tension of the reaction medium(γ_{mix}) such that the apparent surface tension(γ_{app}) of the reaction medium now becomes greater than the critical surface energy(γ_c) of the porous substrate thereby inhibiting spontaneous flow or seepage of the reaction medium through the

porous substrate. This increase in the surface tension of the reaction medium may be accomplished by changes in the reaction conditions such as temperature or by the addition of another component, preferably inert to the desired reaction, to the reaction medium that increases γ_{app}, e.g. a solvent with high surface tension, an additive such as a salt or the like. (3) Adding an immiscible liquid (immiscible under the desired reaction conditions and, if necessary or desirable, inert to the reaction conditions) with a relatively high surface tension(γ_i) and density greater than that of the reaction medium such that it provides for an intermediate barrier between the porous substrate and the reaction medium. Examples of such immiscible liquids with appropriate characteristics and physical properties would include, but are not limited to, water/ether, DMSO/hexane, methylene chloride/water and the like. Those skilled in the art will recognize other binary liquid systems as well as ternary and higher order systems. (4) The application of a net positive partial pressure of an inert gas (inert under the desirable reaction conditions) "downstream" of the porous substrate such that the applied gas is of sufficient pressure to hold-up and prevent flow of the reaction medium through the porous substrate.

Low surface energy (or oleophobicity) may be conferred to the porous substrate by a number of different means including, but not limited to, the following: (1) Coating the substrate with oligomeric or polymeric materials with functionality such that the functionality is favorably dispositioned at the solid-liquid interface of the reaction medium and porous substrate. The selection of coating material(s) and associated functionality will depend upon the desirable γ_c. Coating materials include, for example, fluorocarbons and hydrocarbons and the like containing oligomers and polymers. One preferred coating are a combination of perfluoro compounds The oligomeric or polymeric coating may be preformed or prepared in situ. The coating may be cross-linked by thermal, chemical, or radiational techniques

commonly practiced by those skilled in the art. Alternatively, coating materials of relatively high γ_c, may be further modified and converted to lower γ_c by attachment of the appropriate chemical functionality, providing that the relatively high γ_c materials have attachment sites appropriate for conversion. (2) Many porous substrates have existing or convertible sites appropriate for treatment and conversion to relatively low γ_c materials. Attachment to these sites on the porous substrate may be accomplished by treatment with the appropriate fluorocarbon and hydrocarbon and the like containing reagent(s) that confer low γ_c to the porous substrate. (3) Any combination of the above for tailoring and designing γ_c for use in the chemical reaction(γ_{mix}) of interest.

The surface tension of solvents(γ_s), reaction mixtures(γ_{mix}), immiscible liquids(γ_i), and changes in the surface tension of the reaction medium(γ_{app}), under a variety of temperatures and reaction conditions can be readily determined by such common techniques as tensiometry or other techniques commonly known in the art.

All or part of the reaction medium or components of the reaction medium in the reaction-well device may be drained by lowering the effective surface energy of the reaction medium below the critical surface energy of the oleophobic surface on the substrate. This can be accomplished in a number of ways, for example, by lowering the surface tension of the reaction medium, (γ_{mix}), such that the apparent surface tension of the reaction medium(γ_{app}), now becomes sufficiently small relative to the critical surface energy(γ_c) of the oleophobic surface of the porous substrate thereby providing for spontaneous flow of the reaction medium through the porous substrate. Alternatively; the reaction-well device may be drained by employing a pressure differential across the permeable barrier either by application of a vacuum "downstream" of the porous material or by the application of

pressure "upstream" of the porous material or by eliminating any net applied partial pressure, or by applying centrifugal force either by use of a centrifuge or other suitable instrumentation.

The lowering of the surface tension of the reaction medium, (γ_{app}) may be accomplished by changes in the reaction conditions such as temperature, or by the addition of another component (inert to the desired reaction) to the reaction medium that lowers γ_{mix} (e.g. a solvent with low surface tension or the like, an additive such as a salt or surfactant or the like which lowers the surface tension).

Examples

The invention can further be illustrated, but is not to be limited, by the following examples.

Example 1:

A glass fiber filter (GF/F, Whatman, Inc.) was dipped into a Fluorad® solution (3M, ID # FC-722) and allowed to saturate. Excess Fluorad was drained and the filter was air dried. The filter was then cured for 15 minutes at a temperature of 100°C.

The treated filter was incorporated into a polypropylene microplate having 96 wells of 2 mL each. A group of three wells was filled with each of twenty six solvents and the

microplate was left to drain for 2 hours. The results are illustrated in Table 1.

Table 1.

Solvent	Results
1,1,2,2-Tetrachloroethane	Retained
1-Butanol	Retained
1-Propanol	Retained
Acetone	Partially drained
Acetonitrile	Retained
Chloroform	Retained
Conc. Ammonium hydroxide/water (1:10)	Retained
Dimethylformamide	Retained
Dimethylsulfoxide	Retained
Ethanol	Retained
Ethyl Acetate	Drained
Glacial Acetic acid/water (1:10)	Retained
Heptane	Partially drained
Hexane	Drained
iso-Octane	Drained
Iso-Propanol	Partially drained
Methanol	Retained
Methyl ethyl ketone	Partially drained
Methylene chloride	Retained
Mineral oil	Retained
n-Hexadecane	Retained
Pentane	Drained
p-Xylene	Retained
Tetrahydrofuran	Drained
Toluene	Retained
Water	Retained

As a control, the same twenty-six solvents were added to wells of a microplate containing an untreated glass fiber filter (GF/F, Whatman, Inc.) substrate. All wells had completely drained in one hour except for mineral oil, the most viscous, which was slowly draining.

Example 2.

A glass fiber filter (GF/F, Whatman, Inc.) was dipped into mixture of 40 mL Aversin KFC ® (Henkel Performance Chemicals), 10 mL Repellan HY-N ® (Henkel Performance Chemicals), 0.5 grams citric acid, and water to 1 liter, to saturate it. Excess solution was drained. The filter was then cured for 30 minutes in an oven at a temperature of 130°C.

Example 3:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, 1.0 mL methylene chloride was added to each of twelve wells. No liquid drained from the wells after two hours at room temperature.

Multiple additions of 0.2 mL pentane were made to 6 of the wells, followed by mixing and a five minute period to observe any leakage. Slow drainage began only after the third addition (a total of 0.6 mL pentane added to 1.0 mL methylene chloride.

Example 4:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, 1.0 mL methylene chloride was added to each of twelve wells.

Pentane (1.0 mL) was added to each of three of the wells. Dripping began within 15 seconds and all the liquid (2 mL) had drained within 75 minutes. No liquid drained from the wells containing only methylene chloride after four hours.

Example 5:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, pentane was added to a dry well. The well was completely drained within ten Minutes.

Water was then added to the same (drained) well. The water did not drain, showing that the filter was not damaged by the pentane.

Example 6:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, methanol (1.0 mL) was added into each of 6 wells. After 70 minutes none had passed through the filter. Tetrahydrofuran (1.0 mL) was added to three of the wells, all of which began to drip within another hour. The wells containing only methanol still did not drip.

Tetrahydrofuran (1.0 mL) was placed into a dry well and began dripping within 10 minutes. The well was completely drained within 1.5 hours.

Example 7:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, methanol (1.0 mL) was added into each of 6 wells. After 25 minutes none had passed through the filter. Trifluoroacetic acid (0.5 mL) was added to three of the wells, all of which began dripping within fifteen minutes. The wells containing only methanol still did not drip.

Trifluoroacetic acid (0.5 mL) was placed into a dry well and began dripping within 1 minute. The well was completely drained within 25 minutes.

Example 8:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, pentane (1.0 mL) was added into 2 dry wells and 2 wells already containing an immiscible lower phase of 0.2 mL of water. Both wells containing only pentane began to drip within one minute and completely drained within 10 minutes. The wells containing the water barrier did

not drip after 1 hour. Acetone (0.4 mL) was added to the water layer in one well and the well contents were mixed. This well began to drip within 10 minutes. The remaining well containing water and pentane was drained by vacuum.

While the invention has been described with reference to the preferred embodiment thereof, it will be appreciated by those of ordinary skill in the art that modifications can be make to the structure and form of the invention without departing from the spirit and scope thereof.

CLAIMS

Claim 1. A reaction-well device comprising a filter plate having one or more wells and a base comprised of a selectively permeable barrier.

Claim 2. The reaction-well device of claim 1 wherein said selectively permeable barrier is comprised of a porous substrate having an low energy surface.

Claim 3. The reaction-well device of claim 2 wherein said porous substrate is selected from the group consisting of glass fiber filters GF/x where x= A, B, C, D, and F (designating different porosities), polypropylene, nylon, PTFE, PVDF, and cellulose.

Claim 4. The reaction-well device of claim 1 wherein said low energy surface is comprised of a coating applied to said porous substrate.

Claim 5. The reaction-well device of claim 4 wherein said low energy surface coating is selected from the group consisting of fluorocarbons and hydrocarbons containing oligomers and polymers.

Claim 6. The reaction-well device of claim 1 wherein said low energy surface is comprised of a covalent modification of said porous substrate.

Claim 7. A method for performing chemical reactions in a reaction mixture comprising one or more reactants in the reaction-well device of claim 1 comprising the steps of:

a) filling said one or more wells of said reaction-well device with the reaction mixture, wherein the surface tension of the reaction mixture is sufficiently higher than the critical surface energy of the selectively permeable barrier of said reaction-well device to inhibit flow of said reaction mixture out of said one or more wells;

b) draining said one or more wells.

Claim 8. The method of claim 7 wherein the draining of step b) is achieved by lowering the surface tension of the reaction mixture.

Claim 9. The method of claim 8 wherein the surface tension of the reaction mixture is lowered by the addition of an other reactant.

Claim 10. The method of claim 9 wherein said other reactant is selected from the group consisting of a solvent, a salt, and a surfactant.

Claim 11. The method of claim 8 wherein the surface tension of said reaction mixture is lowered by the alteration of reaction conditions.

Claim 12. The method of claim 11 wherein the surface tension of said reaction mixture is lowered by the alteration of temperature.

Claim 13. The method of claim 7 wherein the draining of step b) is achieved by the application of a pressure differential across said selectively permeable barrier.

Claim 14. The method of claim 7 wherein the draining of step b) is achieved by the application of centrifugal force.

Claim 15. A method for performing chemical reactions in a reaction mixture comprising one or more reactants in the reaction-well device of claim 1 comprising the steps of:

1) placing a liquid which is immiscible with said reaction mixture in said one or more wells in a sufficient quantity to form a liquid barrier between said selectively permeable barrier and said reaction mixture

2) filling said one or more wells of said reaction-well device with the reaction mixture, wherein the flow of said reaction mixture out of said one or more wells is inhibited by said immiscible liquid barrier;

3) draining said one or more wells.

Claim 16. The method of claim 15 wherein the draining of step 3) is achieved by lowering the surface tension of said immiscible liquid barrier.

Claim 17. The method of claim 16 wherein the surface tension of said immiscible liquid barrier is lowered by the addition of an other reactant

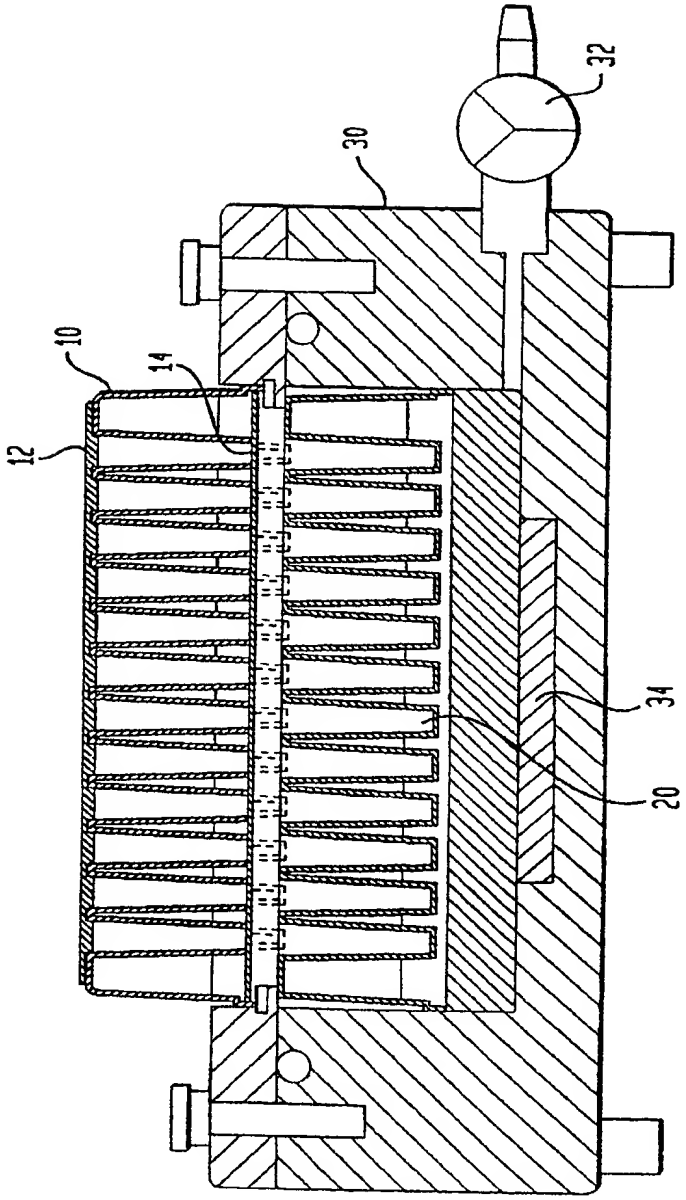
Claim 18. The method of claim 17 wherein said other reactant is selected from the group consisting of a solvent, a salt, and a surfactant.

Claim 19. The method of claim 15 wherein the surface tension of said reaction mixture is lowered by the alteration of reaction conditions.

Claim 20. The method of claim 19 wherein the surface tension of said reaction mixture is lowered by the alteration of temperature.

wherein, the draining of step b) is achieved by lowering the surface tension of the liquid barrier.

FIG. 1



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/58, 68.1, 101, 102, 104; 435/39, 287, 292, 311; 436/177, 809

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,219,528 A (CLARK) 15 June 1993, see entire document.	1-3,7
Y		4-6,8-20
X	US 5,141,719 A (FERNWOOD et al) 25 August 1992, see entire document.	1-3,7
Y		4-6,8-20
X	US 5,108,704 A (BOWERS et al) 28 April 1992, see entire document.	1-3,7
Y		4-6,8-20
X	US 5,039,493 A (OPRANDY) 13 August 1991, see entire document.	1-3,7
Y		4-6,8-20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 DECEMBER 1997	Date of mailing of the international search report 29 JAN 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer HAROLD Y. PYON Telephone No. (703) 308-0651

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18046

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 4,948,564 A (ROOT et al) 14 August 1990, see entire document.	1-3,7 ---------- 4-6,8-20
X ---- Y	US 4,902,481 A (CLARK et al) 20 February 1990, see entire document.	1-3,7 ---------- 4-6,8-20
X ---- Y	US 4,493,815 A (FERNWOOD et al) 15 January 1985, see entire document.	1-3,7 ---------- 4-6,8-20
Y	US 4,777,021 A (WERTZ et al) 11 October 1988, see entire document.	1-20
Y	US 5,227,137 A (MONTI et al) 13 July 1993, see entire document.	1-20
Y	US 4,927,604 A (MATHUS et al) 22 May 1990, see entire document.	1-20
Y	US 4,246,339 A (COLE et al) 20 January 1981, see entire document.	1-20
A	US 4,824,791 A (EKHOLM et al) 25 April 1989, see entire document.	1-20